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PRESENT AND FUTURE ANTIINFLAMMATORY STRATEGIES FOR THE TREATMENT OF ASTHMA

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Introduction

The concept of asthma as an inflammatory disease of the lung has developed over the last 5-7 years. This can be attributed to the availability of bronchoalveolar lavage and endobronchial tissue for histological and biochemical analysis. In a similar way, the approach to the treatment of the condition has shifted from using symptomatic forms of medication to prescribing drugs that may directly influence the underlying pathogenetic mechanisms. Preventing and diminishing inflammation should be the target of treatment and a new generation of drugs are currently being developed to attempt this without the deleterious side effects experienced with oral steroid medication. We shall try to give a short outline of bronchial inflammation and then

discuss different treatment strategies for this problem.

Bronchial Inflammation and Airway Hyperresponsiveness

In addition to intermittent airflow obstruction, asthma is characterized by the presence of bronchial hyperresponsiveness (BHR). This can be defined as an increase above normal in both the ease and magnitude of airway narrowing on exposure to non-sensitizing bronchoconstrictive stimuli (1). While the precise relationship between BHR and airway inflammation is still not certain, animal studies and limited observations in human asthma have provided evidence that increased BHR is related to the degree of inflammation in the airways (2). The concept of BHR is relevant to this discussion because it is often used as an indirect measure of airway inflammation and of the response to antiinflammatory medication.

Inflammatory changes are present in the airways of asthmatic patients, even those with only mild disease and asymptomatic asthmatics may have significant airway inflammation as shown by endobronchial biopsies with histology (3). In young adults asthma represents a special type of "allergic" inflammation characterized by eosinophil and lymphocyte infiltration coupled to epithelial damage or shedding (3-5). Eosinophils contain basic proteins such as major basic protein and cationic protein which may contribute towards epithelial injury (6), increased permeability and exposure of sensory nerve endings which can be stimulated by inflammatory mediators to cause bronchoconstriction. Microvascular leakage with edema formation is a constant feature of all inflammation and also of asthma (4). It leads to a proportionately greater increase in airway resistance when airways smooth muscle contracts, and is probably instrumental in causing temporary irreversible airway obstruction and BHR. Various inflammatory mediators have been implicated in asthma. These include histamine, prostaglandin D_2 and the sulphidopeptide leukotrienes LTC_4, LTD_4 and LTE_4 (6-8). These autocoids are released from mast cells and play an important role in the early phase of asthma (EAR) (9). Their role in causing the late phase of asthma (LAR) is less certain but available evidence suggests an important role for eosinophils in releasing platelet-activating factor (PAF), oxygen radicals, LTC_4 and tissue damaging basic proteins (10,11).

In summary, the histological features of asthma are compatible with a mast cell and eosinophil-mediated inflammatory response. In addition to causing smooth muscle contraction and edema, inflammation causes damage to the ciliated epithelium and the laying down of cross-linked collagen (scar tissue) within the airway wall. On the evidence that asthma has an inflammatory basis and that avoidance of the inducing stimulus is not possible, it seems logical to treat all but the mildest forms of the disease with antiinflammatory drugs.

Treatment of Inflammation in Asthma

Corticosteroids

Corticosteroids have been used to treat asthma for more than 30 years and are the mainstay of medication in many asthmatics. This drug does inhibit the allergen-induced LAR and acquired increases in BHR probably by suppressing components of inflammation. Possible ways in which inflammation may be reversed or prevented by corticosteroids are shown in Table I.

Table I: Possible modes of action of corticosteroids.

1. Reduced synthesis and release of newly formed mediators, *e.g.*, LTB_4 and PAF through secretion of lipocortin.
2. Modulation of cytokine production.
3. Prevention of β-receptor down-regulation.
4. Stabilizing pulmonary microcirculation and decreasing microvascular permeability.
5. Inhibition of excessive mucus production.
6. Stabilizing lysosomal membranes (high concentrations only).

Oral corticosteroids were used initially before inhaled preparations became available. Oral methylprednisolone has been shown to reduce BHR and probably airway inflammation in a dose of 16 mg daily for 7 days (12). However, the side effects of oral corticosteroids such as suppression of the hypothalamic-pituitary-adrenal axis, obesity, hypertension and increased infections precludes their long-term use in most asthmatics.

The development of inhaled corticosteroids heralded a new era in the treatment of asthma. Inhalation delivers the drug directly to the area of pathology with very little systemic absorption and consequent side effects. These drugs are more effective than oral steroids in reducing BHR. Several recent studies have shown that inhaled beclomethasone dipropionate (BDP) and budesonide reduce mast cell and eosinophil populations in the airways, the cells responsible for the early and late phase inflammatory

events. This is dose-related and it may take several weeks for maximal effects to be established (13, 14). Inhaled beclomethasone diproprionate (BDP) in a dose of 2 mg per day abolishes the late response, whereas lower doses give lesser protection (13). Inhaled corticosteroids can be used to replace oral steroids in up to 78% of patients, and can probably be given for many years without any diminution of effect (14). The recent introduction of higher dose BDP preparations has produced a further increase in efficacy in those patients refractory to lower doses. Two milligrams of BDP is the upper limit at which some systemic effects from the swallowed portion may be observed.

It is clear that in adults the antiinflammatory properties of topical corticosteroids make them the medication of first choice for most symptomatic asthmatics. However, because of the prompt bronchodilating effects and because symptoms are relieved immediately patients prefer beta-stimulants. By contrast, inhaled corticosteroids have no direct bronchodilating action and patients are thus less inclined to take them regularly and prophylactically. A number of consensus meetings on asthma management indicate that current clinical practice will have to change from using increasing doses of inhaled beta-stimulants, to the use of inhaled corticosteroids as first-line treatment (15,16). In this regard patient education to instill in asthmatics an awareness of the importance of prophylaxis in asthma via regular use of medication is vital. This is important because in those with poorly controlled asthma chronic inflammation in the airways has been shown to lead to structural and irreversible changes. Thus, it seems appropriate to suppress the inflammation effectively over long periods of time.

Sodium cromoglycate

Sodium cromoglycate (SCG) has traditionally been believed to prevent mast cell degranulation via a membrane stabilizing effect. This may be brought about by the phosphorylation of a protein that results in blocking ionic calcium transport across the cell membrane (17). Prevention of the release of mast cell products such as histamine, PGD_2 and LTC_4 accounts for the action of this drug on the EAR which is IgE and mast cell-dependent. SCG has a wide variety of other suppressive actions on inflammatory cells including macrophages, eosinophils, platelets and neutrophils that might account for the suppressive action of this drug on the allergic LAR. In addition, some evidence suggests that it may exert a neural effect, suppressing the activity of sensory nerve endings since it blocks reflex constrictor stimuli such as bradykinin, SO_2 and subfreezing air (18,19).

SCG is a very safe form of medication and probably the best first-line prophylactic antiinflammatory medication in pediatric practice. However, in most adult asthmatics it has been replaced by inhaled corticosteroids and nedocromil sodium because of their greater potency and more effective antiinflammatory properties.

Nedocromil sodium

This drug has a similar profile of action to SCG, although in most challenge studies it is more potent and has a wider antiinflammatory profile. It protects against antigen-induced bronchoconstriction as well as exercise-induced asthma (EIA) and other nonspecific stimuli (20,21). The mode of action is not understood but as with SCG may involve inhibition of mediator release from mast cells and leukocytes infiltrating the airways. Its position within the antiinflammatory armamentarium is in the prophylactic treatment of mild to moderate adult asthmatics prior to using topical corticosteroids or as an adjunct to topical corticosteroids when these drugs are being used in high doses.

Antihistamines

Histamine is released from mast cells and causes bronchoconstriction and vasodilatation. There are three receptors for histamine, *i.e.*, H_1, H_2 and H_3, of which only H_1-receptors are currently known to be important in asthma. Different antihistamines have in the past been tried in asthma but have only demonstrated minimal effects. Recently the development of specific H_1-receptor antagonists such as astemizole, cetirizine, loratidine, terfenadine and azelastine, has rekindled interest in this group of drugs. Both terfenadine and astemizole inhibited immediate bronchoconstriction to allergen by up to 50%, but did not prevent the development of BHR (22,23). Azelastine has a variety of potentially useful actions pertinent to asthma. It antagonizes 5-hydroxytryptamine and leukotriene D_4 (LTD_4) as well as inhibiting macrophage activation and release of superoxide radicals from neutrophils (24-26). Cetirizine, a very potent H_1-antagonist has been reported to inhibit eosinophil migration following allergen and PAF challenge of human skin (27). These actions may contribute to a decrease in inflammation in asthma, but further studies are required to determine whether these effects are reflected in clinical efficacy. With the suggestion that drugs such as cetirizine

and azelastine have effects other than blocking H_1-receptors, a re-evaluation of the role of this class of drugs in the treatment of mild to moderate asthma is needed.

Long-acting beta-stimulants

Over the last 20 years the inhaled beta-stimulants have become established as the treatment of choice in acute asthma. They have immediate effects causing significant bronchodilation and are popular with patients due to their rapid onset of detectable effect. Currently available β_2-agonists have a short duration of action and ablates the EAR through a combined effect on airway smooth muscle and mast cells (28). In the past it was believed that the LAR is not diminished by these drugs (29) and that they do not prevent the development of BHR in response to allergen challenge, but this concept may be changing. Recent developments have concentrated on prolonging the duration of action of the β_2-agonists. A study of salmeterol, a new long-acting β_2-agonist has shown significantly better bronchodilation compared to treatment with salbutamol, and no evidence of the development of tachyphylaxis (30). However, further assessment of this drug has shown that it also ablates the LAR; this did not appear to be the result of prolonged bronchodilation and functional antagonism (31). This raises the intriguing possibility that continuous mast cell stabilization over a prolonged period may prevent the influx of neutrophils and eosinophils that constitute the inflammatory changes associated with the LAR. Clearly, further studies are necessary to confirm these findings and to study the effects of long-acting β_2-agonist drugs on the inflammatory processes in clinical asthma.

Frusemide

This drug has been used for many years as a loop diuretic and acts by inhibiting the Na-K-Cl co-transporter in the renal tubules. Recently aerosolized frusemide has been shown to protect against asthma provoked by exercise, ultrasonically nebulized water, inhaled AMP in addition to the allergen provoked EAR and LAR (32-35). Thus, there appear to be similarities between the effects of frusemide and SCG. The mechanism of action of frusemide is unknown, but may include increased synthesis of the bronchodilator PGE_2, inhibition of mast cell mediator release, effects on bronchial blood flow or changes in epithelial ion transport (36). It is conceivable that further studies may show a clinical beneficial effect for inhaled frusemide on bronchial inflammation and at the time of writing, clinical trials are being evaluated.

Leukotriene inhibitors and antagonists

Sulphidopeptide leukotrienes (LTs) are products of mast cells, eosinophils and monocytes/macrophages and have been shown to produce bronchoconstriction in normal as well as asthmatic subjects (37,38), and have been proposed as being of central importance as effector mediators of asthma (39). It has also been suggested that these molecules may have a pivotal role in the pathogenesis of bronchial hyperresponsiveness. Other observations have indicated that some of the actions of PAF may be partly mediated by the leukotrienes (40). Consequently, there has been interest in the development of drugs to either block the receptor for leukotrienes or to prevent their synthesis. Various oral leukotriene antagonists based on the acetophenone structure of FPL-55712 have been tested in normal subjects (41) and in asthmatics (42), but showed only very mild inhibition of the early asthmatic reaction (EAR) and no effect on the LAR. More recently, new classes of highly potent LTD_4 antagonists (such as ICI-204219) have been developed. These drugs are potent bronchodilators and early studies suggest that they may provide appreciable protection against the EAR, LAR and the allergen-provoked increase in bronchial responsiveness. Their evolution in clinical asthma is eagerly awaited. Since LTB_4 and other LTs may contribute to the inflammatory response, inhibition of the 5-lipoxygenase enzyme may be an alternative strategy. Several of these compounds are being developed including MK-886 and A-64077, both of which have been studied in allergen induced asthmatic reactions in man (41,42). Provisional data indicate that these compounds may delay the LAR without protection against the development of BHR (41).

Thromboxane receptor antagonists

There has been considerable interest in this group of drugs because it has been shown that PGD_2, TxA_2 and $PGF_{2\alpha}$ cause smooth muscle contraction through stimulation of a receptor classified as the thromboxane TP receptor (43). In human airways the contractile effects of these prostanoids are probably also mediated by the TP receptors, and by using competitive receptor-blocking drugs it may thus be possible to prevent bronchoconstriction as well as inflammatory sequelae of prostanoid release. It has been shown that a selective thromboxane A_2-receptor antagonist GR-32191 can cause inhibition of PGD_2-induced bronchoconstriction, displacing the concentration response curves to the right 3-50 fold (44). The effect on allergen-induced bronchoconstric-

tion was not as marked and in a single trial little benefit was observed in asthma (44). Clearly further studies are needed to evaluate more potent drugs in different types of asthma.

PAF antagonists

The development of this group of drugs is still at an early stage. PAF causes the release of inflammatory mediators and basic proteins from eosinophils (45). It is also secreted by eosinophils in large quantities and the interaction between PAF and eosinophils may be self amplifying and persistent. *In vivo* experiments in animals have demonstrated that PAF antagonists inhibit eosinophil infiltration into the airways of guinea pigs and inhibits allergen-induced bronchial hyperresponsiveness (46,47). A study in humans used short-term treatment for 3 days with the PAF antagonist BN-52063, a ginkgolide, to study protection against exercise-provoked asthma, and found that it provided partial protection against bronchoconstriction (48). Clinical trials with this drug have failed to confirm its efficacy, but this could be due to its low potency as a PAF antagonist. With the knowledge that PAF serves as an up-regulator of mast cells functions, more potent PAF antagonists deserve further studies. One drug, WEB-2086 has been shown to be highly active in suppressing late phase inflammatory events in allergen-challenge models (49) and is currently being evaluated for its antiasthma effects in clinical disease.

Bradykinin receptor antagonists

Bradykinin and kallidin are generated from kininogens through the action of plasma and tissue kallikrein and may be particularly involved in late phase inflammatory changes involving vascular leakage. Bradykinin and its active metabolites elicit a variety of biological effects including bronchoconstriction, sensory nerve stimulation and vascular leakage. These effects are mediated by at least two classes of receptors (50). Bronchoalveolar levels of kinins increase after allergen challenge (51), and elevated kinin levels have been demonstrated in the plasma of asthmatics (52). Bradykinin and its lysyl derivative kallidin have effects predominantly at a single receptor designated B_2, whereas des-Arg bradykinin is an agonist for the B_1-receptor. Studies of B_2-receptor antagonists have thus far only been conducted in allergic sheep (53). As predicted from the mediator profile of bradykinin the use of an antagonist (NPC-567) appeared to have no effect on the EAR but to attenuate the LAR (53). This may represent a potentially novel approach to the management of bronchial inflammation and further studies are required to assess the clinical value of these observations.

Methotrexate

Methotrexate is an antagonist of folic acid and has potent antiinflammatory effects even in low doses. For this reason it has gained acceptance for the treatment of rheumatoid arthritis and psoriasis, causing few side effects and minimal toxicity (54). It has also been tried in severe corticosteroid-dependent asthmatics and a significant steroid-sparing effect was observed (55). Long-term studies over 1-2 years have shown similar beneficial effects at doses between 15-10 mg per week and with relatively benign toxic effects (56). Methotrexate may be of value in severe chronic asthma to decrease morbidity associated with oral corticosteroids, but at this stage there are no indications for its use in non-steroid dependent patients because of its potentially serious hematological and hepatic side effects.

Cyclosporin

There are at least five autoimmune diseases in which cyclosporin has been consistently effective, namely uveitis, psoriasis, diabetes mellitus, rheumatoid arthritis and some types of nephropathy (57). Through its binding to cyclophilin (proline isomerase) it inhibits $CD4^+$ T-cell lymphokine production, and may be beneficial in some diseases because of the antiinflammatory effect. Recent evidence suggests that cytokines secreted by the TH2-lymphocyte subtype and mast cells, interleukin 3 (IL-3), IL-4, IL-5 and IL-10 are important in maintaining the mast cell and eosinophil inflammatory response in asthma. *In vitro* studies have also demonstrated inhibition of histamine and PGD_2 release from human lung mast cells by cyclosporin (58), and therefore on theoretical grounds it may thus be a useful drug in asthma. Clinical trials are currently being undertaken to evaluate its potential in severe steroid-resistant asthma. Side effects, particularly renal and hepatic damage, are likely to be the important limiting factors in the future use of this class of drug.

Colchicine

A recent study using low doses of colchicine in moderate asthmatics has shown some benefit (59). However, pulmonary function was not improved and the importance of the various immunomodulatory effects observed are not known.

Dietary supplementation with fish oil lipids

Ingestion of omega-3 polyunsaturated fatty acids such as docosapentaenoic acid and eicosapentaenoic acid have been shown to decrease LTB_4 production by neutrophils and to decrease *in vitro* chemotactic responses (60). Eicosapentaenoic acid is also metabolized to TxA_3 and LTB_5 which have diminished biological activity (61). These fish oil lipids may therefore have antiinflammatory potential and have been used experimentally to study the effect of diet on the asthmatic response. In a relatively short-term trial dietary enrichment with eicosapentaenoic and docosapentaenoic acids did not affect non-specific airway responsiveness or the severity of asthma (62), but an attenuation of the late response to antigen provocation was demonstrated (63). Generation of LTB_4 from neutrophils by a calcium ionophore was decreased by 47% and neutrophil chemotactic reponses by 50% (63). No improvement in peak expiratory flow (PEF), symptoms and bronchodilator requirements were found although the time of treatment may have been too short (10 weeks) to achieve resolution of inflammation and for a change in clinical variables to occur. Thus, although theoretically attractive the role of this type of dietary treatment in the clinical management of asthma remains to be defined.

Implementing Drug Treatment

Many of the treatment strategies for inflammation that have been discussed are only in the early stages of clinical development and use. However, given the proven efficacy of antiinflammatory forms of medication to modify BHR and other clinical manifestations of asthma, it seems imperative that modes of management involving a high dependence on β_2-agonists which were promoted over the last 2 decades be changed. In all but the mildest disease prevention of and decreasing bronchial inflammation should be the primary aims of treatment. This will require a change in attitude of patients as well as physicians. Patient education, possibly through the establishment of asthma clinics, can contribute to a better understanding of the disease and how it should be managed. The patient's physician should refrain from unthinkingly prescribing only a β_2-agonist to all new asthmatics and to consider the probable benefits of antiinflammatory forms of treatment. Self management is a concept in asthma which can serve to foster a better understanding of the illness and to decrease the need and expense of multiple visits to the doctor (64). Self management strategies also help to integrate patients into their communities and leads to a better acceptance of this chronic disease by family and friends of the patient. Prophylactic drugs and PEF monitoring are key components of meaningful self management strategies (65).

Conclusions

Antiinflammatory treatment has become a priority in the management of asthma. The next decade promises exciting new developments in this field and in the elucidation of the pathogenetic mechanisms involved as well as new drug developments. In this new era the search for an effective new non-steroidal antiasthma drug will be a priority as will a change in attitude to conform to the old adage that "prevention is better than cure".

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